UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE

Nys Willem Siebers

CHANGES OF PAIN INTENSITY RESULTS WITH DIFFERENT FOLLOW-UP TIMES IN RANDOMIZED CONTROLLED TRIALS OF OSTEOARTHRITIS: A CASE STUDY OF CELECOXIB

Diploma Thesis

Academic Year:

2018/2019

Mentor:
Prof. Livia Puljak, MD, PhD

Split, July 2019

Table of Contents

ACKNOWLEDGEMENT

First of all, I would like to thank my mentor Prof. Livia Puljak, MD, PhD. Without her help this Thesis would not have been possible. Additionally, I want to thank Assist. Prof. Filipa Markotic MD, PhD who has helped me collect data and was always available when I was in doubt about anything.

Lastly, I would also like to thank my parents, Dr. Derk Siebers and Elke Siebers as well as my sister Merle Siebers who have always supported me throughout my professional as well as private life. Without them I would not be the person I am today.

List of abbreviations

BMI – Body Mass Index

CDSR – Cochrane Database of Systematic Reviews

CFB – Change from Baseline

COX1/COX2 – Cyclooxygenase 1/Cyclooxygenase 2

DALY´s – Disability Adjusted Life Years

ICTRP – International Clinical Trials Registry Platform

IPR – Inadequate pain relieve

NSAID´s – Non-steroidal anti-inflammatory drugs

OA – Osteoarthritis

RCT´s – Randomized Controlled Trials

SD – Standard deviation

SMD – Standardized mean difference

VAS – Visual Analog Scale

WOMAC – Western Ontario and Mc Master Universities Osteoarthritis Index

1. INTRODUCTION

1.1. Osteoarthritis

Osteoarthritis is a chronic degenerative disease predominantly affecting weight bearing joints in the human body. It is currently suggested to be a heterogeneous disease caused by a combination of excessive wear and tear as well as abnormal joint mechanics and inflammation. The concept of its pathophysiology is still unfolding. Through progress in molecular biology it evolved from being viewed as a cartilage-limited disorder to a multifactorial disease affecting the whole joint. This intricate relationship between local and systemic factors modulates its structural features and clinical presentation leading to a common final pathway of joint destruction [1].

The pain underlying Osteoarthritis is of heterogeneous nature. An interplay between local pathologic changes, neuroplastic changes as well as general factors like adipositas, diabetes mellitus and psychosocial factors have been identified to be responsible for the development of chronic joint pain [2]. Presumably arising from mechanical sensitization of joint nociceptors through inflammation, pain perception progresses in response to a complex series of neurophysiologic events. They are comprised of sensitization of peripheral and central pathways as well as reduction of descending conditioning pain modulation and atrophy of cortical areas involved in pain processing [2]. Moreover, a subset of patients pain phenotype indicates a neuropathic component [3]. All those mechanisms combined likely skew the relationship between the extend of tissue injury and perceived pain in any situation but the acute one. Current evidence suggests osteoarthritic damage predisposes to pain but there is little correlation between the severity of pain and the extend of joint damage [4].

Osteoarthritis most commonly results from a combination of modifiable and non-modifiable risk factors including obesity, trauma, increasing age, genetic predisposition and gender. Those affected classically suffer from pain, stiffness and limited range of motion ultimately leading to joint destruction and the necessity to perform joint replacement surgery [5].

Osteoarthritis is the single most common cause of chronic disability in older adults [5]. A report from the Global Burden of Disease 2010 study indicated that of the 291 conditions listed, hip and knee osteoarthritis was ranked globally as the 11th highest contributor to global disability and the 38th highest in disability-adjusted life years (DALYs) [6]. It is estimated that 10-15% of all adults aged over 60 have some degree of osteoarthritis with a prevalence that is higher among women than men [7] The increasing lifespan of the general population combined with an expected rise in obese patients can potentially aggravate the global impact of this disease.

According to the United Nations, by 2050, 130 million people will suffer from OA worldwide of whom 40 million will be severely disabled by the disease [8]

Treatment of osteoarthritis is directed at pain alleviation, improvement of physical function and the delay of joint replacement surgery. Treatment modalities are generally divided into non-pharmacological, pharmacological and surgical options. Non-pharmacologic options include: patient education, application of heat and cold, weight loss, low to moderate intensity exercise, physical therapy and mechanical joint unloading through braces or foot wear [5].

Pharmacologic options include medicines such as acetaminophen, topical and oral non-steroidal anti-inflammatory drugs (NSAIDS), tramadol and intra-articular injections like corticosteroids or autologous Plasma. Additionally, there are certain nutritional supplements, foremost glucosamine, which has shown some beneficial results in osteoarthritis clinical trials [9]. New potential targets for analgesic therapy have been identified. The antibody tanezumab targeting nerve growth factor; sensory proteins at the nociceptive nerve endings such as the activating TRPV and ASIC channel. Additionally, axonal channels such as voltage-gated Sodium channels, various potassium channels as well as inhibitory opioid and cannabinoid receptors [10].

Surgical procedures that are used for symptomatic treatment of osteoarthritis include arthroscopy for debridement, osteotomy or fusion [11]. Unfortunately, the only definite treatment is joint replacement which, due to limited durability of modern implants, is often preceded by years of chronic analgesic use and significant disability. After successful arthroplasty, as defined by prosthesis-related outcomes, still a proportion of about 9% of patients with hip and about 20% of patients with knee replacements have unfavorable long-term results with patient-centered pain outcomes over a follow up from 3 month to 5 years after surgery [12]. In order to address the time period from onset of disease to joint replacement, patients need therapies that provide adequate pain relief over an extended period of time.

1.3. Celecoxib

Celecoxib is a drug belonging to the class of coxibs, recommended for symptomatic treatment of osteoarthritis. Like conventional NSAIDS, they work by inhibiting the cyclooxygenase enzyme which converts arachidonic acid into prostaglandins which further mediate pain and inflammation amongst other functions. The cyclooxygenase enzyme has two isoforms active in humans. The constitutive COX-1 is present, for example in the endothelium, stomach and kidney, whereas COX-2 is induced by pro-inflammatory cytokines and endotoxin in cells in vitro and at inflammatory sites in vivo [13]. In contrast to conventional NSAIDS which inhibit both isoforms of the enzyme non-selectively, coxibs are relatively more selective for the COX-2 enzyme. Whilst equally efficacious their specificity presumably gives them a more favorable side effect profile. Unfortunately, this has not been confirmed in the Cochrane review "Celecoxib for osteoarthritis" [14].

1.4. Cochrane systematic review

Systematic reviews are secondary research projects in which researchers attempts to gather all the existing empirical evidence that meets pre-specified eligibility criteria in order to answer a specific research question. Methods used for conducting such reviews should be explicit and systematic, striving towards minimization of bias in order to facilitate the production of reliable findings for further decision making [15]. Those reviews are complicated and their results heavily depend on the availability, and even more importantly, the quality of existing clinical trials. The strength of the evidence of the systematic review directly correlates with the quality of included studies. If possible, in a systematic review authors may pool numerical data about treatment effects through the process of meta-analysis. Through this process systematic reviews are able to summarize all the existing clinical research concerning a particular research question [16].

Cochrane systematic reviews are considered gold standard in evidence synthesis field. They are produced by Cochrane, a global independent network of health practitioners, researchers, patient advocates and people interested in health from over 130 countries. Cochrane has more than 37000 contributors that collectively respond to the challenge of making the vast amount of evidence available through research applicable for consumers. Cochrane is a not-for profit organization whose mission is to produce high quality evidence that is free from commercial sponsorship and other conflicts of interests in order to facilitate evidence-based decision making in the health-care setting [17].

Cochrane systematic reviews are systematic reviews in the field of health-care published in the Cochrane Database of Systematic Reviews (CDSR), the leading journal for systematic reviews in health care [18]. Cochrane has developed a meticulous methodological approach for producing systematic reviews. There are five types of systematic reviews in CDSR: reviews of the effects of interventions, reviews of diagnostic test accuracy, methodology reviews, qualitative reviews, and methodology reviews [19]. Additionally, CDSR publishes overviews of systematic reviews, i.e. systematic reviews that summarize systematic reviews [20]. All those reviews follow a clear structured review model which is provided in the Cochrane Handbook for Systematic Reviews of Interventions [21]. Guidance available in the Cochrane Handbook should guarantee consistency of methods used in Cochrane reviews.

1.5. Cochrane review about celecoxib for osteoarthritis

Cochrane review "Celecoxib for osteoarthritis" was published in the CDSR in 2017 [14]. The review showed no statistically significant difference between celecoxib and placebo for serious adverse effects, gastro-intestinal events (perforations, ulcers bleeds) and cardiovascular events (myocardial infarction, stroke). Due to high risk of bias and imprecision it is to be noted that evidence level was downgraded to very low quality [14].

The same review reached several other conclusions relevant for clinical decision making: Firstly, they noted that benefits of celecoxib were not much different than placebo or other NSAIDS. Furthermore, they noticed decreasing efficacy of celecoxib for pain with longer duration of included studies, expressed as decreasing standardized mean difference [14].

On the contrary, previous data from the research group of prof. Andrew Moore indicated that there is high correlation of pain scores measured with a visual-analog-scale (VAS) after 2 and 6 weeks of treatment with VAS pain scores at 12 weeks in randomized controlled trials (RCTs) about rheumatoid arthritis and osteoarthritis [22]. This group of authors concluded that early analgesic response measuring pain scores with VAS beyond 2 weeks of treatment with a particular NSAID is likely to be predictive of pain VAS response at 12 weeks, and that these results have implications for future study design of randomized controlled trials RCTs).

Namely, the authors suggest that appropriate treatment duration for studies of efficacy in this setting could be shorter, for example 6 weeks instead of 12 weeks [22].

Since efficacy data for pain from the Cochrane review “Celecoxib for Osteoarthritis” would imply different conclusion compared to conclusions of Moore and colleagues, the aim of this study was to conduct more comprehensive analysis of efficacy data for pain in RCTs about celecoxib for osteoarthritis over different follow-up times.

2. OBJECTIVES

The aim of this Thesis was to conduct more comprehensive analysis of efficacy data for pain in RCTs about celecoxib in osteoarthritis. The purpose of this is to improve long-term management of pain for patients suffering from osteoarthritis by guiding clinical decision making, and to create evidence that will inform design of future RCTs about osteoarthritis.

3. METHODS

3.1. Study Design

This was a retrospective primary methodological study, in which publicly available data from published RCTs were analyzed. Therefore, permission of the ethics committee for data collection was not necessary.

3.2. Inclusion of studies

We included RCTs analyzing the effects of celecoxib on pain intensity measured with the Visual Analog Scale (VAS) and/or the Western Ontario and McMaster University Osteoarthritis Index (WOMAC), and comparing celecoxib with placebo. We did not limit studies based on duration, and we had no limits regarding language. Search strategy used for retrieving eligible studies was described in the Cochrane review "Celecoxib for Osteoarthritis", and we used for this analysis all eligible RCTs that were found in the literature while conducting our Cochrane review [14].

3.3. Types of Intervention

Oral celecoxib 200 mg daily (either as 200 mg once daily or 100 mg twice daily) versus Placebo. Dosage of 200 mg was used because it is the recommended dosage.

3.4. Types of outcome measures

The outcome measure was pain. Pain scales used were the VAS scale and the WOMAC osteoarthritis index pain sub score.

3.5. Extraction of data

We extracted the following data from eligible RCTs: study ID (first author, year), study duration in weeks, follow-up times used in the study for measuring pain intensity, efficacy data for pain measured with VAS and/or WOMAC for all reported follow-up times (mean, standard deviation, number of participants). If the study reported data only in figures, we extracted data from figures using the Plot Digitizer software [23]. We extracted data in the way they were presented, including baseline data, final end-of-study data and change from baseline.

3.6. Data analysis

Since the majority of data were reported as change from baseline, for the studies that reported baseline data and absolute values at different time points, we calculated change from baseline using baseline data and time point data using methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions [24].

We used random-effects meta-analyses for synthesis of pain scores for different pain outcome measures and different follow-up time points that were reported in included studies. Standardized mean differences (SMDs) were used to report the data. We used Review Manager (RevMan) for data analyses [25].

3.7. Data imputations

Missing standard deviations (SDs) were imputed only from baseline data or other follow-up data of the same manuscript. We did not do any imputations for missing SDs from other manuscripts. For studies that have shown only absolute results, we calculated change from baseline.

4. RESULTS

Included studies

We included 35 RCTs in this analysis. All included RCTs were published as full-text manuscripts. We did not find any eligible RCTs that were published as conference abstracts, or that were unpublished. The list of included studies is shown in Table 1.

Table 1. List of included studies

No	Included studies
1.	Asmus 2014 Study 1 [26]
2.	Asmus 2014 Study 2 [26]
3.	Bensen 1999 [27]
4.	Bingham 2007 Study 1 [28]
5.	Bingham 2007 Study 2 [28]
6.	Birbara 2006 Study 1 [29]
7.	Birbara 2006 Study 2 [29]
8.	Boswell 2008 Study a [30]
9.	Boswell 2008 Study b [30]
10.	Clegg 2006 [31]
11.	Conaghan 2013 [32]
12.	De Lemos 2011 [33]
13.	Essex 2016 [34]
14.	Fleischmann 2005 [35]
15.	Gibofsky 2003 [36]
16.	Gordo 2017 [37]
17.	Hochberg 2011 Study 307 [38]
18.	Hochberg 2011 Study 309 [38]
19.	Kivitz 2001 [39]
20.	Lee M 2017 [40]
21.	Lehman 2005 [41]
22.	Mc Kenna 2001a [42]
23.	Mc Kenna 2001b [42]
24.	Pincus 2004 PACES-a [43]
25.	Pincus 2004 PACES-b [43]
26.	Reginster 2017 [44]

27.	Rother 2007 [45]
28.	Schnitzer 2011 [46]
29.	Sheldon 2005 [47]
30.	Smugar 2006 Study 1 [48]
31.	Smugar 2006 Study 2 [48]
32.	Tannenbaum 2004 [49]
33.	Williams 2000 [50]
34.	Williams 2001 [51]
35.	Wittenberg 2006 [52]

We excluded 14 studies due to reasons listed in the Table 2.

Table 2. List of excluded studies

No	Excluded studies	Reason for exclusion
1.	Bianchi 2003 [53]	fewer than 50 participants in each arm
2.	Bianchi 2007 [54]	fewer than 50 participants in each arm
3.	Detrembleur 2005 [55]	fewer than 50 participants in each arm
4.	EUCTR2005-002772-14-GB	Outcome data is the same as in Schnitzer 2011
5.	EUCTR2011-005398-22-ES	Results are not available
6.	Gallelli 2013 [56]	fewer than 50 participants in each arm
7.	Leeb 2004 [57]	fewer than 50 participants in each arm
8.	Mastbergen 2010 [58]	fewer than 50 participants in each arm
9.	NCT01768520	Results of study could not be found. Stated to use Korean WOMAC
10.	Ozgocmen 2005 [59]	fewer than 50 participants in each arm
11.	Sampalis 2012 [60]	fewer than 50 participants in each arm
12.	Simon 1998 [61]	SD not reported, and could not be imputed from other results reported in this manuscript
13.	Tascioglu 2004 [62]	fewer than 50 participants in each arm
14.	Trudeau 2015 [63]	fewer than 50 participants in each arm

Results from the Schnitzer 2011 study and results posted for the study EUCTR2005-002772-14-GB registered at the International Clinical Trials Registry Platform (ICTRP) had exactly the same results, up to two decimals. Even though the Schnitzer 2011 study reported in the manuscript that the study was registered only on ClinicalTrials.gov (NCT00154219), details in these two registrations on ICTRP and on ClinicalTrials.gov are identical, and therefore we considered that these are the same studies, and we did not include these data two times in our analysis.

Effect sizes

Time points for results available for data analysis in included studies that have reported pain using VAS are shown in Table 3, while the time points for results in studies that reported pain using WOMAC is shown in Table 4.

Table 3. Time points with results for pain measured with visual analogue scale (VAS) in included studies

Time point	Study name
2 weeks	Bensen 1999
	Bingham 2007 study 1
	Bingham 2007 study 2
	Fleischmann 2005
	Kivitz 2001
	Lehman 2005
	McKenna 2001b
	Sheldon 2005
	Simon 1998
	Tannenbaum 2004
	Williams 2000
	Williams 2001
3 weeks	Gibofsky 2003
	McKenna 2001a
4 weeks	Bingham 2007 study 1
	Bingham 2007 study 2
	Lehman 2005

	Sheldon 2005
	Schnitzer 2011
	Tannenbaum 2004
30 days	Reginster 2017
6 weeks	Asmus 2014 study 1
	Asmus 2014 study 2
	Bensen 1999
	Essex 2016
	Gibofsky 2003
	Gordo 2017
	Kivitz 2001
	McKenna 2001b
	Pincus 2004 PACES-a
	Pincus 2004 PACES-b
	Williams 2000
	Williams 2001
8 weeks	Bingham 2007 study 1
	Bingham 2007 study 2
	Lehman 2005
	Schnitzer 2011
	Sheldon 2005
	Tannenbaum 2004
9 weeks	Conaghan 2013
	DeLemos 2011
12 weeks	Bensen 1999
	Bingham 2007 study 1
	Bingham 2007 study 2
	DeLemos 2011
	Kivitz 2011
13 weeks	Fleischmann 2005
	Lehman 2005
	Reginster 2007

	Schnitzer 2011
	Sheldon 2005
	Tannenbaum 2004
14 weeks	Pincus 2004 PACES-a
	Pincus 2004 PACES-b
15 weeks	Fleischmann 2005
26 weeks	Reginster 2017

Table 4. Time points with results for pain measured with Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) in included studies

Time point	**Study name**
1 week	Boswell 2008 Study A
	De Lemos 2011
	Wittenberg 2006
2 weeks	Bensen WG 1999
	Birbara 2006 Study 1
	Birbara 2006 Study 2
	Boswell 2008 Study A
	Boswell 2008 Study B
	Conaghan 2013
	De Lemos 2011
	Fleischmann 2005
	Kivitz 2001
	Lehman 2005
	Smugar 2006 Study 1
	Smugar 2006 Study 2
	Tannenbaum 2004
3 weeks	De Lemos 2011
	Lee M 2017
4 weeks	Birbara 2006 Study 1
	Birbara 2006 Study 2
	Boswell 2008 Study A
	Boswell 2008 Study B
	Mastbergen 2010

	Schnitzer 2011
	Smugar 2006 Study 1
	Smugar 2006 Study 2
6 weeks	Asmus 2014 Study 1
	Asmus 2014 Study 2
	Birbara 2006 Study 1
	Birbara 2006 Study 2
	Boswell 2008 Study A
	Conaghan 2013
	De Lemos 2011
	Essex 2016
	Gibofsky 2003
	Gordo 2017
	Hochberg 2011 Study 307
	Hochberg 2011 Study 309
	Lee M 2017
	Rother 2007
	Williams 2000
	Williams 2001
8 weeks	Boswell 2008 Study B
	Schnitzer 2011
9 weeks	Conaghan 2013
	De Lemos 2011
12 weeks	Bensen WG 1999
	Bingham 2007 Study 1
	Bingham 2007 Study 2
	Boswell 2008 Study B
	Conaghan 2013
	De Lemos 2011
	Hochberg 2011 Study 307
	Hochberg 2011 Study 309
	Kivitz 2001
13 weeks	Fleischmann 2005

	Lehman 2005
	Schnitzer 2011
	Sheldon 2005
	Tannenbaum 2004
24 weeks	Clegg 2006

We imputed SD from other parts of the manuscript in 7 studies (Bensen 1999, Kivitz 2001, McKenna2001a, Lehman 2005, Schnitzer 2011, Tannenbaum 2004, De Lemos 2001). There were 5 studies that showed only absolute values, and for which we calculated change from baseline (Bensen 1999, Gibofsky 2003, Reginster 2007, Williams 2000, Williams 2001).

We made 20 meta-analyses based on the included studies. There were 2 meta-analyses with only one study included. Other meta-analyses had from 2 to 18 included studies. The list of meta-analyses conducted is shown in Table 5 and 6 for pain VAS and pain WOMAC respectively.

As shown in Tables 5 and 6, SMDs had decreasing trend from earliest to latest analyzed time points, both for VAS and for WOMAC, indicating that the effect of celecoxib as an intervention was decreasing with time. However, all these studies were of short duration – the longest follow-up time used in studies that reported pain using VAS was 13 weeks, while the longest follow-up time reported for WOMAC pain was 24 weeks.

Table 5. Standardized mean difference (SMD) for pain in studies that compared celecoxib versus placebo, measured with visual analog scale

Time point	SMD and 95% CI	Heterogeneity	Number of studies	Number of participants
2 weeks	-0.50 (-0.63 to -0.38)	81%	12	6047
3 weeks	-0.53 (-0.73 to -0.32)	0%	2	408
4 weeks	-0.45 (-0.55 to -0.35)	54%	6	3910
30 days	-0.13 (-0.32 to 0.07)	Not applicable	1	399
6 weeks	-0.44 (-0.55 to -0.32)	71%	12	4141
8 weeks	-0.41 (-0.52 to -0.30)	64%	6	3910
12 weeks	-0.48 (-0.64 to-0.31)	66%	5	1822
13 weeks	-0.23 (-0.30 to -0.17)	0%	7	3763

Table 6. Standardized mean difference (SMD) for pain in studies that compared celecoxib versus placebo, measured with WOMAC scale

Time point	SMD and 95% CI	Heterogeneity	Number of studies	Number of participants
1 week	-0.32 (-0.46 to - 0.18)	0%	3	828
2 weeks	-0.37 (-0.44 to -0.29)	53%	13	6146
3 weeks	-0.37 (-0.53 to -0.20)	0%	2	618
4 weeks	-0.30 (-0.39 to -0.21)	23%	7	3052
6 weeks	-0.35 (-0.43 to -0.27)	45%	16	5128
8 weeks	-0.29 (-0.49 to -0.08)	63%	2	1165
9 weeks	-0.24 (-0.37 to -0.11)	0 %	2	862
12 weeks	-0.32 (-0.40 to -0.25)	13%	9	3468
13 weeks	-0.27 (-0.33 to -0.20)	0%	5	3393
24 weeks	-0.13 (-0.28 to -0.03)	Not applicable	1	631

Forest plots for individual meta-analyses are shown in Figures 1-19.

	Celecoxib			Placebo				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Bensen WG 1999	-28.61	9.2635	197	-13.57	38.1841	203	8.8%	-0.54 [-0.74, -0.34]
Bingham 2007 study 1	-21.49	16.8021	241	-7.56	18.2547	127	8.3%	-0.80 [-1.03, -0.58]
Bingham 2007 study 2	-23.3	24.4359	247	-11.16	16.2665	117	8.3%	-0.55 [-0.77, -0.32]
Fleischmann 2005	-20.3	23.07	444	-15.9	24.29	231	9.6%	-0.19 [-0.35, -0.03]
Kivitz 2001	-24.4	17	207	-11.8	14.9	217	8.8%	-0.79 [-0.99, -0.59]
Lehman 2005	-17.5	20.4	420	-11.3	18.74	424	10.0%	-0.32 [-0.45, -0.18]
McKenna 2001b	-33.4	27	199	-20.4	25.5	200	8.8%	-0.49 [-0.69, -0.29]
Sheldon 2005	-23.9	14.17	393	-14	13.18	382	9.8%	-0.72 [-0.87, -0.58]
Tannenbaum 2004	-17.5	20.5	481	-9.1	19.3	243	9.6%	-0.42 [-0.57, -0.26]
Williams 2000	-26	24.4354	222	-12.6	28.2696	231	9.0%	-0.51 [-0.69, -0.32]
Williams 2001	-21.1	24.3179	231	-14.2	24.7856	243	9.1%	-0.28 [-0.46, -0.10]
Total (95% CI)			**3282**			**2618**	**100.0%**	**-0.50 [-0.63, -0.38]**

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 52.68$, df = 10 (P < 0.00001); $I^2 = 81\%$

Test for overall effect: Z = 8.02 (P < 0.00001)

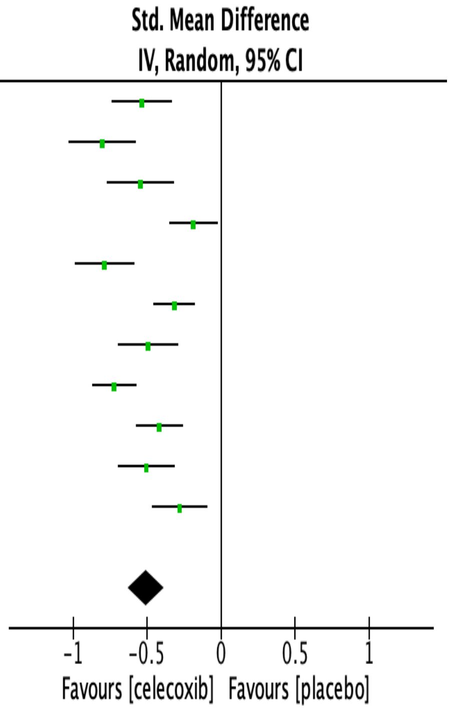

Figure 1. Comparison celecoxib versus placebo, outcome: pain VAS, 2 weeks

	Celecoxib			Placebo				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Gibofsky 2003	-28.63	28.8702	189	-14.53	28.1201	96	67.8%	-0.49 [-0.74, -0.24]	
McKenna 2001a	-33.41	16.2	63	-24.3	13.8	60	32.2%	-0.60 [-0.96, -0.24]	
Total (95% CI)			**252**			**156**	**100.0%**	**-0.53 [-0.73, -0.32]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 5.03 (P < 0.00001)

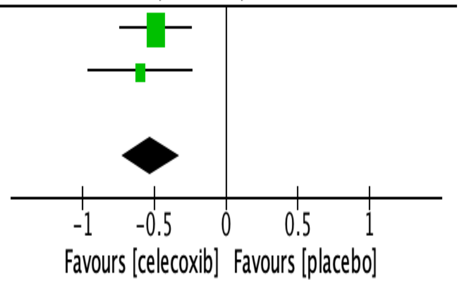

Figure 2. Comparison celecoxib versus placebo, outcome: pain VAS, 3 weeks

	Celecoxib			Placebo				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bingham 2007 study 1	-24.87	22.4474	241	-10.59	19.9142	127	12.2%	-0.66 [-0.88, -0.44]	
Bingham 2007 study 2	-25.82	23.8773	247	-15.14	18.3579	117	12.0%	-0.48 [-0.70, -0.26]	
Lehman 2005	-21.95	20.04	420	-15.27	18.74	424	19.7%	-0.34 [-0.48, -0.21]	
Schnitzer 2011	-28.8	15.46	419	-20.5	15.37	416	19.5%	-0.54 [-0.68, -0.40]	
Sheldon 2005	-22.4	14.17	393	-16.2	13.18	382	19.0%	-0.45 [-0.60, -0.31]	
Tannenbaum 2004	-21	20.5	481	-14.9	19.3	243	17.7%	-0.30 [-0.46, -0.15]	
Total (95% CI)			**2201**			**1709**	**100.0%**	**-0.45 [-0.55, -0.35]**	

Heterogeneity: Tau² = 0.01; Chi² = 10.80, df = 5 (P = 0.06); I² = 54%
Test for overall effect: Z = 9.02 (P < 0.00001)

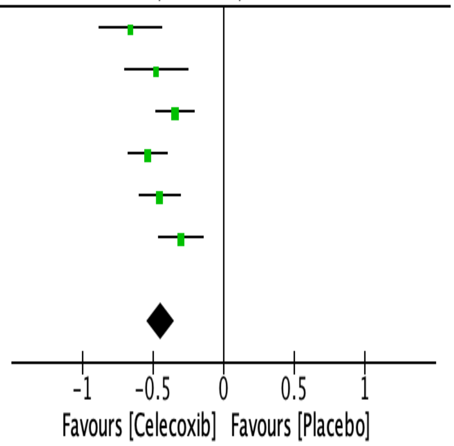

Figure 3. Comparison celecoxib versus placebo, outcome: pain VAS, 4 weeks

	Celecoxib			Placebo				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Reginster 2017	-23.1	20.9464	195	-20.5	19.996	204	100.0%	-0.13 [-0.32, 0.07]	
Total (95% CI)			**195**			**204**	**100.0%**	**-0.13 [-0.32, 0.07]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 1.26 (P = 0.21)

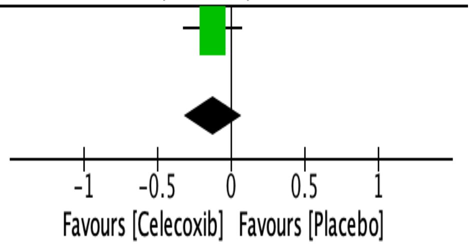

Figure 4. Comparison celecoxib versus placebo, outcome: pain VAS, 30 days

Study or Subgroup	Celecoxib Mean	Celecoxib SD	Celecoxib Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Asmus 2014 study 1	-27.3	29	186	-14.9	27.12	184	8.7%	-0.44 [-0.65, -0.23]
Asmus 2014 study 2	-28	29.24	194	-24.6	27.27	186	8.9%	-0.12 [-0.32, 0.08]
Bensen WG 1999	-29.16	9.2635	197	-18.11	38.1841	203	8.9%	-0.39 [-0.59, -0.20]
Essex 2016	-37.1	22	121	-33.6	19.801	58	6.4%	-0.16 [-0.48, 0.15]
Gibofsky 2003	-34	27.4955	189	-21.2	26.4545	96	7.8%	-0.47 [-0.72, -0.22]
Gordo 2017	-34.5	24.6312	122	-28.4	25.5181	56	6.4%	-0.24 [-0.56, 0.07]
Kivitz 2001	-25.1	17	207	-13.2	14.9	217	9.0%	-0.74 [-0.94, -0.55]
McKenna 2001b	-34.9	28.1	199	-23.1	28	200	8.9%	-0.42 [-0.62, -0.22]
Pincus 2004 PACES-a	-19	25.6964	181	-10.5	25.1806	172	8.7%	-0.33 [-0.54, -0.12]
Pincus 2004 PACES-b	-21.8	25.96	189	-7.6	26.09	182	8.7%	-0.54 [-0.75, -0.34]
Williams 2000	-26.4	16.6	182	-13	15.1	146	8.3%	-0.84 [-1.07, -0.61]
Williams 2001	-24.2	16.5	231	-17.4	16.5	243	9.3%	-0.41 [-0.59, -0.23]
Total (95% CI)			**2198**			**1943**	**100.0%**	**-0.44 [-0.55, -0.32]**

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 37.49$, df = 11 ($P < 0.0001$); $I^2 = 71\%$

Test for overall effect: $Z = 7.30$ ($P < 0.00001$)

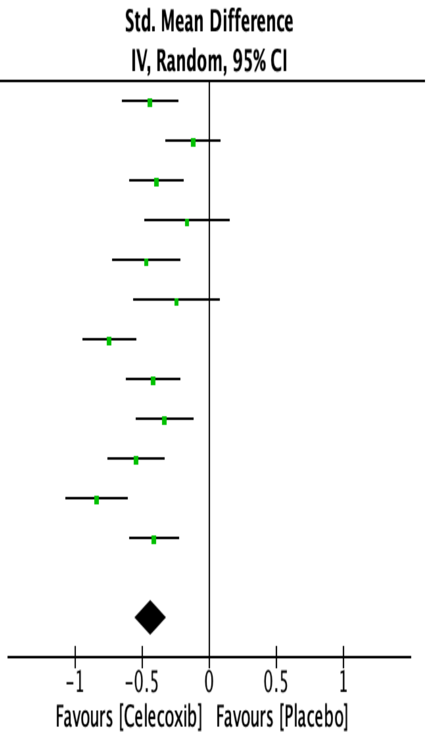

Figure 6. Comparison celecoxib versus placebo, outcome: pain VAS, 6 weeks

Study or Subgroup	Celecoxib Mean	Celecoxib SD	Celecoxib Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bingham 2007 study 1	-24.65	24.9415	241	-13.05	20.283	127	13.1%	-0.49 [-0.71, -0.28]
Bingham 2007 study 2	-26.95	23.7352	247	-16.21	18.9002	117	12.8%	-0.48 [-0.70, -0.26]
Lehman 2005	-26.54	23.65	420	-20.34	23.97	424	19.1%	-0.26 [-0.40, -0.12]
Schnitzer 2011	41.7	15.46	419	49.9	15.37	416	18.9%	-0.53 [-0.67, -0.39]
Sheldon 2005	-25.6	14.17	393	-18.8	13.18	382	18.5%	-0.50 [-0.64, -0.35]
Tannenbaum 2004	-24.8	24.7	481	-18.4	26.1	243	17.6%	-0.25 [-0.41, -0.10]
Total (95% CI)			**2201**			**1709**	**100.0%**	**-0.41 [-0.52, -0.30]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 13.91$, $df = 5$ ($P = 0.02$); $I^2 = 64\%$
Test for overall effect: $Z = 7.30$ ($P < 0.00001$)

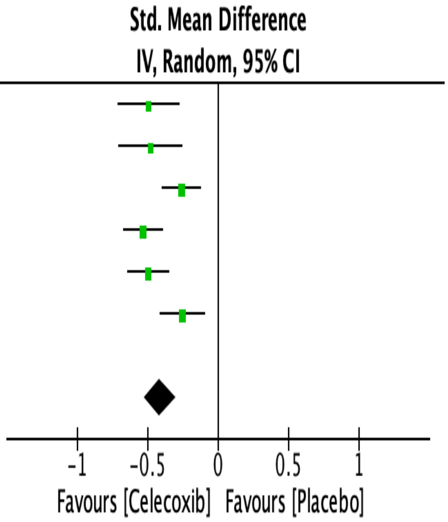

Figure 7. Comparison celecoxib versus placebo, outcome: pain VAS, 8 weeks

Study or Subgroup	Celecoxib Mean	Celecoxib SD	Celecoxib Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bensen WG 1999	-27.07	9.2635	197	-16.74	38.1841	203	21.1%	-0.37 [-0.57, -0.17]
Bingham 2007 study 1	-24.83	23.1402	192	-15.47	20.283	85	17.5%	-0.42 [-0.68, -0.16]
Bingham 2007 study 2	-27.84	23.8773	202	-16.27	19.6748	117	19.0%	-0.51 [-0.75, -0.28]
DeLemos 2011	-33.4	29.8466	202	-23.8	29.6985	200	21.2%	-0.32 [-0.52, -0.13]
Kivitz 2001	-23.3	17	207	-11.1	14.9	217	21.2%	-0.76 [-0.96, -0.57]
Total (95% CI)			**1000**			**822**	**100.0%**	**-0.48 [-0.64, -0.31]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 11.91$, $df = 4$ ($P = 0.02$); $I^2 = 66\%$
Test for overall effect: $Z = 5.68$ ($P < 0.00001$)

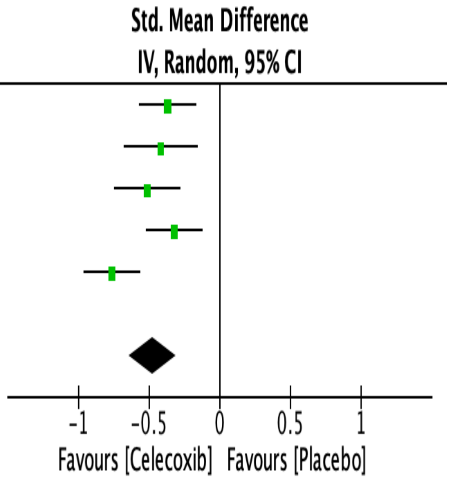

Figure 8. Comparison celecoxib versus placebo, outcome: pain VAS, 12 weeks

Study or Subgroup	Celecoxib Mean	Celecoxib SD	Celecoxib Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Fleischmann 2005	-27.4	27.72	444	-21.3	26.33	231	16.8%	-0.22 [-0.38, -0.06]
Lehman 2005	-26.6	23.65	368	-21.4	23.97	360	20.1%	-0.22 [-0.36, -0.07]
Reginster 2017	-31.7	22.9343	182	-29	21.9381	188	10.3%	-0.12 [-0.32, 0.08]
Schnitzer 2011	-33.4	27	327	-24.3	26.05	287	16.7%	-0.34 [-0.50, -0.18]
Sheldon 2005	-24.1	26.4	393	-18.1	25.51	382	21.4%	-0.23 [-0.37, -0.09]
Tannenbaum 2004	-25.2	24.7	401	-19.8	26.1	200	14.7%	-0.21 [-0.38, -0.04]
Total (95% CI)			**2115**			**1648**	**100.0%**	**-0.23 [-0.30, -0.17]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.07$, df = 5 (P = 0.69); $I^2 = 0\%$
Test for overall effect: Z = 6.96 (P < 0.00001)

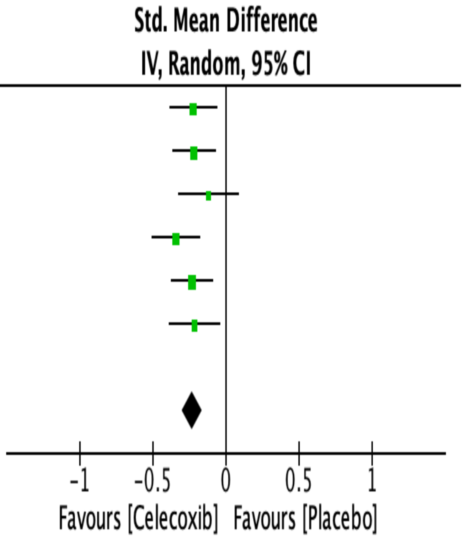

Figure 9. Comparison celecoxib versus placebo, outcome: pain VAS, 13 weeks

Study or Subgroup	Celecoxib Mean	Celecoxib SD	Celecoxib Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Boswell 2008 Study A	-12.32	15.5754	105	-8.36	15.8788	101	25.7%	-0.25 [-0.53, 0.02]
DeLemos 2011	-99.57	96.1	202	-67.53	103.5	200	49.9%	-0.32 [-0.52, -0.12]
Wittenberg 2006	-4	3.3	145	-2.7	3.2	75	24.4%	-0.40 [-0.68, -0.12]
Total (95% CI)			**452**			**376**	**100.0%**	**-0.32 [-0.46, -0.18]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.53$, df = 2 (P = 0.77); $I^2 = 0\%$
Test for overall effect: Z = 4.53 (P < 0.00001)

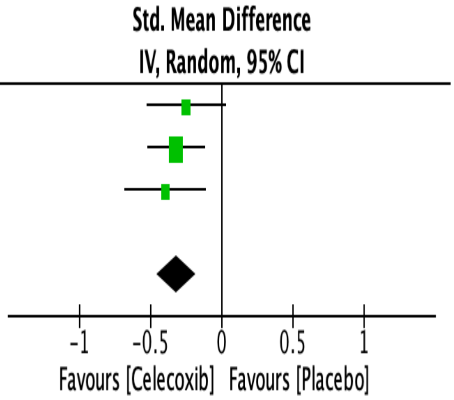

Figure 10. Comparison celecoxib versus placebo, outcome: pain WOMAC, 1 week

	Celecoxib			Placebo				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Bensen WG 1999	-2.92	3.0878	197	-0.83	3.562	203	7.6%	-0.63 [-0.83, -0.42]
Birbara 2006 Study 1	-25.3	53.707	156	-17.72	51.3125	78	5.4%	-0.14 [-0.41, 0.13]
Birbara 2006 Study 2	-24.71	55.0669	164	-19.18	52.56	81	5.5%	-0.10 [-0.37, 0.16]
Boswell 2008 Study A	-14	18.0346	105	-11.9	20.0998	101	5.3%	-0.11 [-0.38, 0.16]
Boswell 2008 Study B	-23.2	19.6614	163	-14.9	18.8674	167	7.0%	-0.43 [-0.65, -0.21]
Conaghan 2013	-0.99	1.2211	233	-0.737	1.2053	227	8.3%	-0.21 [-0.39, -0.02]
DeLemos 2011	-122.39	96.1	202	-87.23	103.5	200	7.7%	-0.35 [-0.55, -0.15]
Fleischmann 2005	-2.9	3.6	444	-1.6	3.1	231	9.3%	-0.38 [-0.54, -0.22]
Kivitz 2001	-2.52	5.1795	207	-0.6	3.6827	217	7.9%	-0.43 [-0.62, -0.24]
Lehman 2005	-2.5	3.17	420	-1.1	3.08	424	10.4%	-0.45 [-0.58, -0.31]
Smugar 2006 Study 1	-33.7	25.1594	447	-22.7	25.8577	146	8.1%	-0.43 [-0.62, -0.25]
Smugar 2006 Study 2	-32.2	25.7091	459	-18.4	24.4949	150	8.1%	-0.54 [-0.73, -0.36]
Tannenbaum 2004	-2.4	3.1	481	-1.4	3.3	243	9.5%	-0.32 [-0.47, -0.16]
Total (95% CI)			**3678**			**2468**	**100.0%**	**-0.37 [-0.44, -0.29]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 25.30$, df = 12 (P = 0.01); $I^2 = 53\%$
Test for overall effect: Z = 9.13 (P < 0.00001)

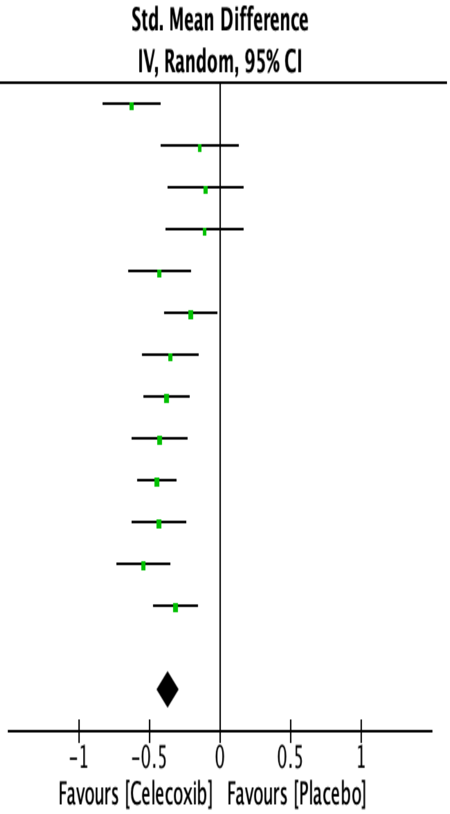

Figure 11. Comparison celecoxib versus placebo, outcome: pain WOMAC, 2 weeks

	Celecoxib			Placebo				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
DeLemos 2011	-141.85	96.1	202	-102.09	103.5	200	67.6%	-0.40 [-0.59, -0.20]
Lee M 2017	-4.4	8.1883	145	-2	7.1622	71	32.4%	-0.30 [-0.59, -0.02]
Total (95% CI)			**347**			**271**	**100.0%**	**-0.37 [-0.53, -0.20]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.28$, df = 1 (P = 0.60); $I^2 = 0\%$
Test for overall effect: Z = 4.43 (P < 0.00001)

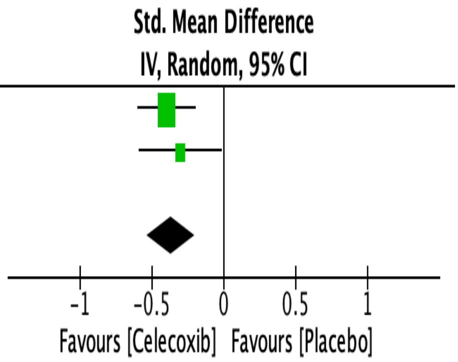

Figure 12. Comparison celecoxib versus placebo, outcome: pain WOMAC, 3 weeks

Study or Subgroup	Celecoxib Mean	Celecoxib SD	Celecoxib Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Birbara 2006 Study 1	-27.2	55.3307	156	-19.17	50.6943	78	9.2%	-0.15 [-0.42, 0.12]
Birbara 2006 Study 2	-29.58	56.3475	164	-21.03	53.73	81	9.5%	-0.15 [-0.42, 0.11]
Boswell 2008 Study A	-19.52	20.5964	105	-15.36	20.6022	101	9.1%	-0.20 [-0.48, 0.07]
Boswell 2008 Study B	-25.61	20.6828	163	-21.11	22.7442	167	13.4%	-0.21 [-0.42, 0.01]
Schnitzer 2011	-3.08	4.28	419	-1.76	3.94	416	25.3%	-0.32 [-0.46, -0.18]
Smugar 2006 Study 1	-35.08	25.1594	447	-25.02	26.5827	146	16.6%	-0.39 [-0.58, -0.21]
Smugar 2006 Study 2	-32.7	26.7804	459	-20.09	26.4545	150	16.8%	-0.47 [-0.66, -0.29]
Total (95% CI)			**1913**			**1139**	**100.0%**	**-0.30 [-0.39, -0.21]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.83$, df = 6 (P = 0.25); $I^2 = 23\%$
Test for overall effect: Z = 6.57 (P < 0.00001)

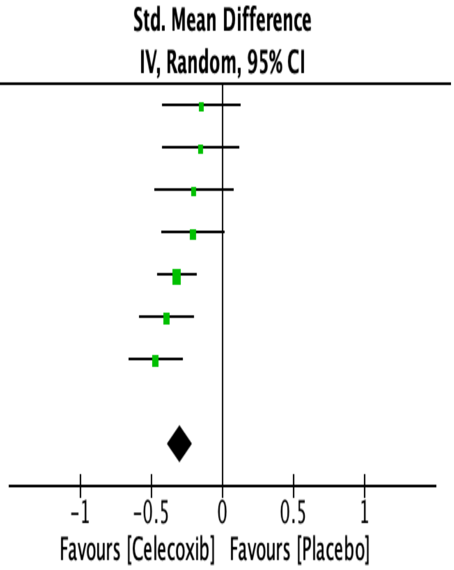

Figure 13. Comparison celecoxib versus placebo, outcome: pain WOMAC, 4 weeks

Study or Subgroup	Celecoxib Mean	Celecoxib SD	Celecoxib Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Birbara 2006 Study 1	-27.3	35.2218	156	-19.24	39.6546	78	5.4%	-0.22 [-0.49, 0.05]
Birbara 2006 Study 2	-28.51	22.9232	164	-20.95	39.69	81	5.5%	-0.26 [-0.52, 0.01]
Boswell 2008 Study A	-19.6	72.5484	105	-16.9	36.883	101	5.4%	-0.05 [-0.32, 0.23]
Conaghan 2013	-1.55	1.3738	233	-1.18	1.5067	227	8.2%	-0.26 [-0.44, -0.07]
DeLemos 2011	-161.91	127.914	202	-118.35	125.865	200	7.7%	-0.34 [-0.54, -0.15]
Essex 2016	-5.6	4.3451	118	-4.3	3.8406	59	4.5%	-0.31 [-0.62, 0.00]
Gibofsky 2003	-4.7	4.1243	158	-2.6	3.9192	64	4.9%	-0.51 [-0.81, -0.22]
Gordo 2017	-3.3	4.5466	151	-1.7	4.1509	78	5.3%	-0.36 [-0.64, -0.09]
Hochberg 2011 Study 307	-40.72	26.5	242	-31.95	26.5	124	7.0%	-0.33 [-0.55, -0.11]
Hochberg 2011 Study 309	-38.99	26.5	244	-35.26	26.5	122	7.0%	-0.14 [-0.36, 0.08]
Lee M 2017	-5.7	8.4291	145	-2.6	7.5835	71	5.1%	-0.38 [-0.66, -0.09]
Rother 2007	-20.7	22.7	109	-12.4	21	102	5.4%	-0.38 [-0.65, -0.11]
Smugar 2006 Study 1	-33	19.1572	367	-22	17.3586	93	6.6%	-0.58 [-0.81, -0.35]
Smugar 2006 Study 2	-30.8	19.799	392	-16.7	17.265	92	6.5%	-0.73 [-0.96, -0.50]
Williams 2000	-2.94	3.6	194	-1.4	3.5	182	7.4%	-0.43 [-0.64, -0.23]
Williams 2001	-2.8	3.4	231	-1.8	3.3	243	8.3%	-0.30 [-0.48, -0.12]
Total (95% CI)			**3211**			**1917**	**100.0%**	**-0.35 [-0.43, -0.27]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 27.16$, df = 15 (P = 0.03); $I^2 = 45\%$
Test for overall effect: Z = 8.52 (P < 0.00001)

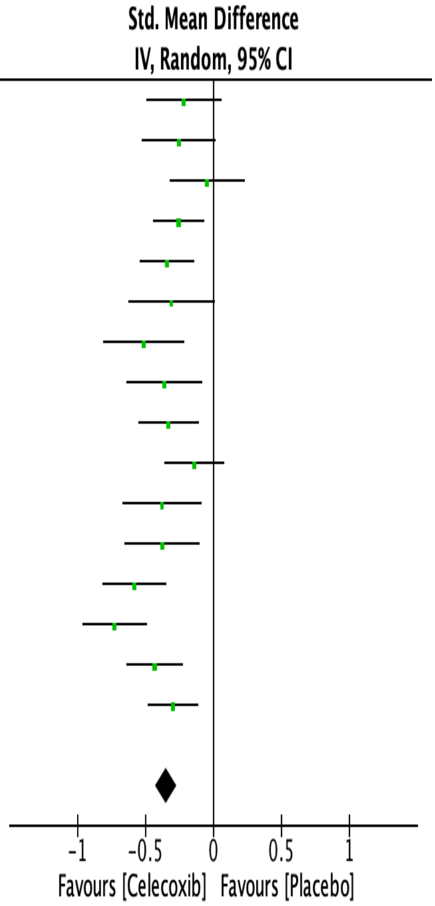

Figure 14. Comparison celecoxib versus placebo, outcome: pain WOMAC, 6 weeks

Study or Subgroup	Celecoxib Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Boswell 2008 Study B	-28.25	23.3639	163	-24.42	24.1657	167	42.2%	-0.16 [-0.38, 0.06]
Schnitzer 2011	-3.64	4.28	419	-2.09	3.94	416	57.8%	-0.38 [-0.51, -0.24]
Total (95% CI)			**582**			**583**	**100.0%**	**-0.29 [-0.49, -0.08]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.73$, df = 1 (P = 0.10); $I^2 = 63\%$
Test for overall effect: Z = 2.68 (P = 0.007)

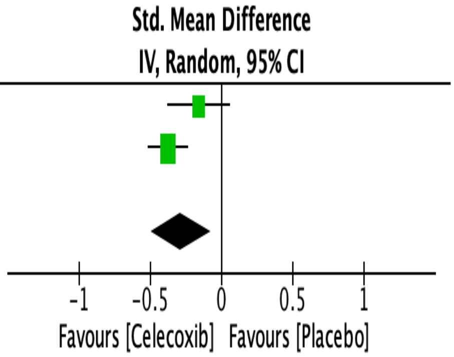

Figure 15. Comparison celecoxib versus placebo, outcome: pain WOMAC, 8 weeks

Study or Subgroup	Celecoxib Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Conaghan 2013	-1.71	1.5264	233	-1.27	1.6573	227	53.2%	-0.28 [-0.46, -0.09]
DeLemos 2011	-160.46	127.914	202	-135.37	125.865	200	46.8%	-0.20 [-0.39, -0.00]
Total (95% CI)			**435**			**427**	**100.0%**	**-0.24 [-0.37, -0.11]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.33$, df = 1 (P = 0.57); $I^2 = 0\%$
Test for overall effect: Z = 3.50 (P = 0.0005)

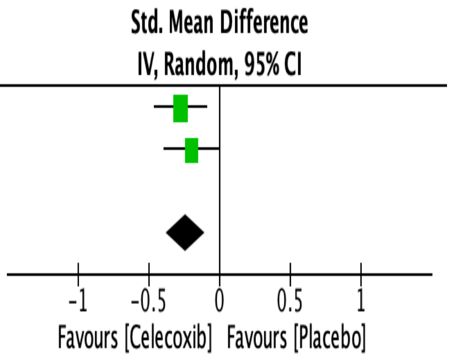

Figure 16. Comparison celecoxib versus placebo, outcome: pain WOMAC, 9 weeks

Study or Subgroup	Celecoxib Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bensen WG 1999	-3.06	4.4914	197	-1.41	3.8469	203	11.9%	-0.39 [-0.59, -0.20]
Bingham 2007 study 1	-24.7	22.9	236	-12.4	24.6	126	10.0%	-0.52 [-0.74, -0.30]
Bingham 2007 study 2	-26.7	24.1	246	-14.6	24.8	112	9.4%	-0.50 [-0.72, -0.27]
Boswell 2008 Study B	-28	23.8746	163	-21.7	21.5812	167	10.2%	-0.28 [-0.49, -0.06]
Conaghan 2013	-1.9	1.62	233	-1.42	1.62	227	13.5%	-0.30 [-0.48, -0.11]
DeLemos 2011	-130	127.914	202	-94.9	125.865	200	12.1%	-0.28 [-0.47, -0.08]
Hochberg 2011 Study 307	-41.8	26.5	242	-35.6	26.5	124	10.2%	-0.23 [-0.45, -0.02]
Hochberg 2011 Study 309	-42.9	26.5	244	-38.4	26.5	122	10.1%	-0.17 [-0.39, 0.05]
Kivitz 2001	-2	4.32	207	-0.8	4.42	217	12.6%	-0.27 [-0.47, -0.08]
Total (95% CI)			**1970**			**1498**	**100.0%**	**-0.32 [-0.40, -0.25]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 9.21$, df = 8 (P = 0.32); $I^2 = 13\%$
Test for overall effect: Z = 8.58 (P < 0.00001)

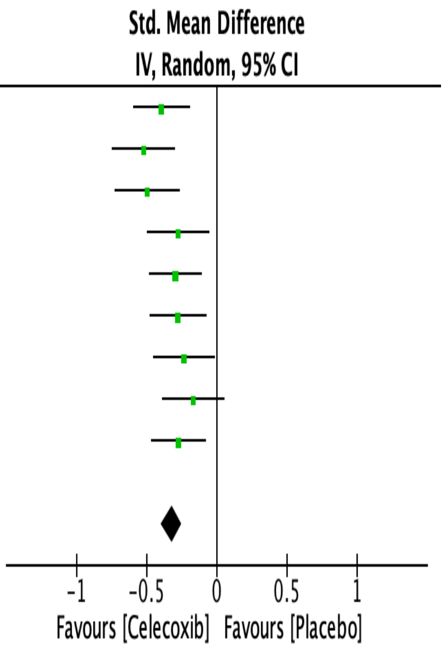

Figure 17. Comparison celecoxib versus placebo, outcome: pain WOMAC, 12 weeks

Study or Subgroup	Celecoxib Mean	Celecoxib SD	Celecoxib Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Fleischmann 2005	-3.5	4.11	444	-2.3	3.9	231	18.6%	-0.30 [-0.46, -0.14]
Lehman 2005	-3.4	3.67	368	-2.5	4.12	360	22.4%	-0.23 [-0.38, -0.08]
Schnitzer 2011	-3.6	4.28	327	-2.2	3.94	287	18.7%	-0.34 [-0.50, -0.18]
Sheldon 2005	-3.4	4.21	393	-2.3	3.84	382	23.8%	-0.27 [-0.41, -0.13]
Tannenbaum 2004	-3.1	3.8	401	-2.4	3.8	200	16.5%	-0.18 [-0.35, -0.01]
Total (95% CI)			**1933**			**1460**	**100.0%**	**-0.27 [-0.33, -0.20]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.07$, df = 4 (P = 0.72); $I^2 = 0\%$

Test for overall effect: Z = 7.54 (P < 0.00001)

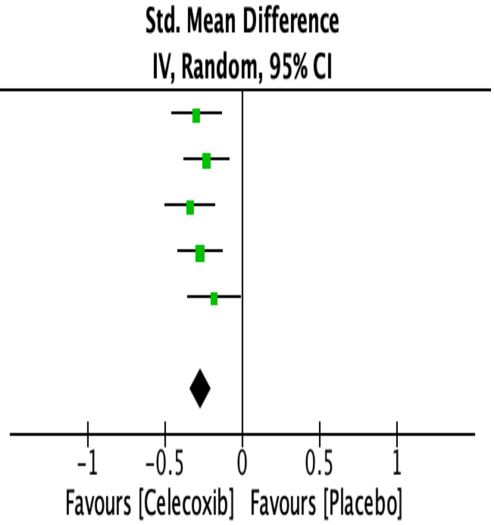

Figure 18. Comparison celecoxib versus placebo, outcome: pain WOMAC, 13 weeks

Study or Subgroup	Celecoxib Mean	Celecoxib SD	Celecoxib Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Clegg 2006	-100	102.9	318	-86.1	114.2	313	100.0%	-0.13 [-0.28, 0.03]
Total (95% CI)			**318**			**313**	**100.0%**	**-0.13 [-0.28, 0.03]**

Heterogeneity: Not applicable

Test for overall effect: Z = 1.60 (P = 0.11)

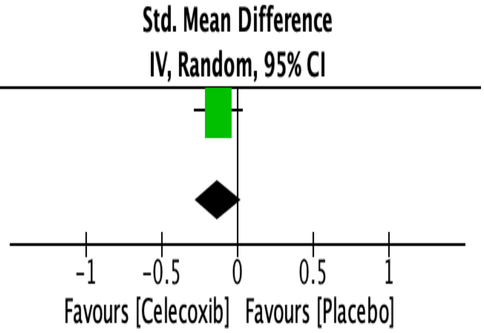

Figure 19. Comparison celecoxib versus placebo, outcome: pain WOMAC, 24 weeks

5. DISCUSSION

In this study we found a decreasing trend of a numerical indicator for efficacy of celecoxib for treatment of pain in studies that compared celecoxib and placebo, and reported pain results with VAS and WOMAC scales. It has to be emphasized that these studies were relatively short, considering the chronic nature of osteoarthritis; the longest follow-up in the group of studies that reported VAS pain was 13 weeks and those that reported WOMAC pain was 24 weeks. There was only one study for data analysis for the domain WOMAC at 24 weeks. Additionally, SMD remained fairly constant with VAS over most follow up times (SMD at 2 weeks: -0.50; SMD at 12 weeks: -0.48) as well as with WOMAC (SMD at 2 weeks: -0.32; SMD at 12 weeks: -0.32). The later follow-up times showed a decreased SMD for VAS at 13 weeks (SMD: -0.23) and for WOMAC at 24 weeks (SMD: -0.13).

This study was conducted because we observed discrepancies between the 2017 Cochrane review on celecoxib for osteoarthritis and results published by Moore et al. [22]. Moore et al. used regression models to assess correlation between efficacy comparing diclofenac, ibuprofen, naproxen, celecoxib or etericoxib with each other or with placebo at 2, 6 and 12 weeks. Their evidence base consisted of 50 RCTs used for analysis. The results suggested that average change from baseline (CFB) of VAS pain at all time-points were highly associated. Therefore, pain VAS at 2 weeks was predictive of pain VAS at 6 and 12 weeks [22]. Similar predictive effects of early response to NSAIDs in predicting late response where demonstrated earlier by Bingham et al. in a pooled analysis of 2 identical 26-week studies testing etericoxib, celecoxib and placebo in patients with OA of the hip and knee. With active treatment 75% of patients who were responders at 2 weeks were also responders at 12 weeks [64]. Both groups analyzed follow-up times up to 12 weeks.

Moore et al. concluded that clinical trials for efficacy of NSAIDs can be shorter as early response is likely associated with late response and early treatment failure is likely to be associated with treatment failure in general [22].

In line with studies of Moore et al. and Bingham et al. this study showed that SMDs observed at 2, 6 and 12 weeks remained relatively constant, for pain measured with both VAS and WOMAC.

However, our data also indicate that efficacy of celecoxib measured with pain VAS decreased from week 2 (SMD: -0.50) to weeks 13 (SMD: -0.23), as well as with pain WOMAC from week 2 (SMD: -0.32) to week 24 (SMD: -0.13).

Based on our findings, we can provide suggestions concerning future designs of RCTs as well as clinical decision-making that are contrary to conclusions of Moore et al. and Bingham et al.

Our results indicate that trialists should conduct studies with longer follow-up times in order to adequately assess efficacy of celecoxib over a prolonged period. In a chronic condition such as OA, for which patient will require adequate analgesic treatment over extended periods, it could be misleading to conduct studies with short follow-up times. The overwhelming majority of the studies included in our analysis was conducted within 13 weeks, with only one that had 24-week follow-up and none longer than that.
Most patients with OA are treated with analgesics for far longer periods than this and a potential decrease in efficacy of celecoxib with longer treatment duration has to be addressed due to the multiple reasons:

Firstly, inadequate pain relief (IPR) could lead to amplification of pain response through maladaptive neuroplastic mechanisms [65]. Secondly, pain is not merely a symptom but also a disease on its own which can manifest with chronic pain leading to significant morbidity and health care related costs [66]. Additionally, almost one half of all patients are dissatisfied with the control of OA pain provided by NSAID therapy, according to a study by Taylor-Stokes et al. from 2013 [67]. In a 2014 prospective multinational longitudinal study about real-world therapies for OA, it was shown that inadequate pain relief is a highly relevant problem among patients with OA. Predictors for IPR included, female sex, higher body mass index (BMI), longer OA duration, bilateral knee OA, depression and diabetes. IPR was associated with functional loss and impaired quality of life [68]. Furthermore, patients with OA presumably prefer medication with a longer treatment effect. This was shown in a study conducted by Oxford University and published in April 2019. Researchers conducted a discrete choice experiment with 300 residents of the United Kingdom with hip and/or knee OA to quantify patients' preferences for the duration of treatment effect relative to treatment benefits and risks. Results showed that pain, severity and duration of treatment effect had the greatest influence on medication preference. This suggests that patients would be willing to take medication which is less effective in relieving pain if the effect of the medication lasts longer. Moreover, participants were willing to accept an increase in the risk of heart attack of 2.6% to increase the duration of the treatment effect from one to 12 month [69]. Similar to results of our study, the authors appealed to future trialists to conduct clinical trials with longer follow-up for investigating treatment effect to evaluate if significant benefit is sustained over time. Duration of treatment effect seems to be an important factor in the medication choices of people with osteoarthritis and therefore should not be dismissed by researchers and physicians.

All in all, it remains unclear how effective NSAIDs are in the treatment of chronic conditions such as OA. It was shown in the 2017 review about celecoxib for osteoarthritis that celecoxib proved only to be negligibly better than placebo. Results from this review suggest that the effectiveness of celecoxib could decrease with treatment duration above 12 weeks.
We appeal to researchers to conduct additional RCTs with longer follow-up times to address this issue. Stratification of patients according to known risk factors for IPR could be helpful in further studies.

Joint pain is complex and yet to be understood thoroughly, especially when chronic. A multi-disciplinary approach in management is crucial in order to provide adequate treatment and improved quality of life.

There remains a compelling need for effective, well-tolerated analgesic drugs in order to limit inadequate therapy for patients with conditions that can lead to the development of chronic pain and all its associated sequelae. There have been significant advances in our understanding of the neurobiology of joint pain in OA. Potentially new targets for novel analgesics have been identified [10].

In addition to clarifying the effectiveness of traditionally used drugs like NSAIDs and coxibs, future research should focus on novel analgesics in order to bridge the gap between our understanding of pain and clinical practice.

Our study had several limitations. We used studies identified in the 2017 Cochrane review, as well as additional studies, but we did not systematically search for all potentially newly published studies. However, despite this lack of additional systematic search, we are not aware of any new studies that have studied efficacy of celecoxib vs. placebo with longer follow-up times than reported in this study. As already indicated in the 2017 Cochrane review about celecoxib for osteoarthritis, included studies had major limitations and evidence quality was poor. Therefore, results should be interpreted with caution. None of the studies in that Cochrane review had low risk of bias for all seven assessed domains. Selection bias was poorly reported in most trials and attrition bias was high in most trials. Additionally, there was selective reporting in about one third of trials.

We did not assess risk of bias in additional studies used in this analysis. Another limitation is that there was only one study available for the analysis of WOMAC at 24 weeks as well as for VAS at 30 days.

Due to involvement of industry sponsors in most of the analyzed trials there is a reason to be reserved because it has been shown that such sponsorship may lead to more favorable results of the intervention. Cochrane review of Lundh et al. included 75 studies that have analyzed whether industry sponsored drug and medical device studies have more favorable results compared to studies without such sponsorship and they found that there is an industry bias which cannot be explained by standard risk of bias assessment. [70]

Patients in most studies included in the Cochrane review on celecoxib for OA were allowed to use rescue medication in case the study medication did not provide adequate pain relieve. This is of course necessary from an ethical standpoint, but concerning adequacy of comparative results this represents a confounding factor. Trialists did not measure amount of rescue medication used by patients and did not include this factor in their analyses of drug efficacy.

Some studies had to be excluded from this analysis because they did not report standard deviation or standard error with their main effect. Additionally, we had trouble obtaining complete data from certain studies as it was not provided in the published study and further requests to study sponsors were not successful. Study authors and sponsors should provide open access to their full data sets in order to make use of complete data sets for future analysis. Furthermore, in trials with multiple follow-up time points, the trialists should not report only results for the final follow-up, but also for all measured follow-ups. Lastly, pain experience in OA patients is complex and potentially not measured adequately by existing measures which are used in current analysis.

6. CONCLUSION

1. It remains unclear how effective celecoxib 200 mg is in comparison to placebo for the treatment of osteoarthritis.

2. Our data indicates that efficacy of celecoxib 200 mg could decrease over longer follow-up times due to decreasing SMDs found at 13 weeks for VAS and at 24 weeks for WOMAC pain scales.

3. Previous research showed a similar trend of efficacy for celecoxib over 12 weeks follow-up. Data from later time points used in our study suggest a decrease of efficacy with longer follow-up times.

4. Current research about use of celecoxib in osteoarthritis is potentially insufficient for patient groups taking Celecoxib for a prolonged period of time.

5. Osteoarthritis is a complex disease with significant socio-economic burden. In order to optimize treatment and reduce disease related negative health outcomes new treatment modalities are needed that bridge the gap between our understanding of Osteoarthritis pain and clinical practice.

7. SUMMARY

Objectives: The aim of this Thesis was to conduct comprehensive analysis of efficacy data for pain in randomized controlled trial RCTs about Celecoxib in osteoarthritis (OA). The ultimate purpose of this study is to improve long-term management of pain for patients suffering from OA by guiding clinical decision making, and to create evidence that will inform design of future RCTs about OA.

Material and Methods: This was a methodological study in which publicly available data from RCTs were analyzed. RCTs analyzing the effects of 200 mg celecoxib vs. placebo on pain intensity with the Visual Analog Scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score were included. Random effect meta-analysis was used for different pain outcome measures and different follow-up times. Standardized mean differences were used to report the data.

Results: We found a decreasing trend of a numerical indicator for efficacy of celecoxib for treatment of pain in RCTs comparing Celecoxib 200 mg to Placebo and reported pain results with the VAS and WOMAC scale. Standardized mean differences remained relatively constant with VAS and WOMAC over most follow-up times. The later follow-up times showed a decreased SMD for VAS at 13 weeks as well as for WOMAC with 24 weeks.

Conclusion: Our data indicates that efficacy of celecoxib 200 mg could decrease over longer follow-up times. Future trials should include assessment at longer follow-up times for adequate assessment of efficacy and safety of celecoxib.

8. CROATIAN SUMMARY

Naslov na hrvatskom jeziku: Promjene intenziteta boli u različitim vremenima praćenja u randomiziranim kontroliranim pokusima o celekoksibu za osteoartritis

Ciljevi: Cilj ove disertacije bio je provesti detaljnu analizu o ishodima koji opisuju intenzitet boli u randomiziranim kontroliranim pokusima (engl. randomized controlled trials; RCTs) o celekoksibu za osteoartritis (OA). Konačni cilj je dati nove informacije za praksu i omogućiti ustroj boljih RCT-ova u budućnosti.

Metode: Provedeno je metodološko istraživanje u kojem su analizirani javno dostupni podatci iz RCT-ova. Uključeni su RCT-ovi koji su analizirali djelotvornost i sigurnost celekoksiba 200 mg u usporedbi s placebom. Intenzitet boli je analiziran vizualno-analognom ljestvicom (engl. Visual-Analog Scale; VAS) i WOMAC ljestvicom (engl. Western Ontario and McMaster Universities Osteoarthritis Index). Provedena je meta-analiza nasumičnih učinaka (engl. random effect meta-analysis) kako bi se analizirao zbirni učinak za različite mjere ishoda u različitim vremenima praćenja. Standardizirane srednje razlike (engl. standardized mean differences; SMD) su korištene za prikaz podataka.

Rezultati: Uočen je trend smanjenja SMD za djelotvornost celekoksiba za liječenje OA prema mjernim instrumentima VAS i WOMAC u kasnijim vremenima praćenja. Pokusi koji su koristili ljestvicu VAS trajali su najviše 13 tjedana, a pokusi koji su koristili ljestvicu WOMAC najviše 24 tjedna.

Zaključak: Dobiveni podatci ukazuju da bi djelotvornost celekoksiba za liječenje boli u OA mogla biti manja s duljim vremenom primjene lijeka. Novi klinički pokusi trebali bi uključiti dulje vrijeme praćenja kako bi se dobili odgovarajući podatci iz istraživanja o dugoročnoj djelotvornosti i sigurnosti celekoksiba u OA koji je kronična bolest

9. CURICULUM VITAE

Personal Data

Name	Nys Siebers
Address	Spinčićeva 25c 21000 Split
Date of Birth	19/08/1990
Place of Birth	Berlin / Germany

Education

2013 - 2019	University of Split, School of Medicine
09/2016	United States Medical Licensing Exam
01/2011-12/2011	Paramedic Training at NAW Berlin
2002-2010	A-levels at Humboldt Gymnasium Berlin

Work experience

04/2016-06/2016	Tutor for Anatomy at Split School of Medicine
01/2013-07/2013	Paramedic at Rettungsdienst Oberhavel GmbH
03/2013-08/2013	First Aid Instructor at NAW Berlin
12/2012-08/2013	Event Paramedic at Medics Berlin
05/2012-11/2012	Paramedic at DRK Freital
06/2011-08/2011	Various internships as part of paramedic training

10. REFERENCES

1. Martel-Pelletier J, Barr AJ, Cicuttini FM, Conaghan PG, Cooper C, Goldring MB, et al. Osteoarthritis. Nat Rev Dis Primers. 2016;2:16072.

2. Schaible HG. Osteoarthritis pain. Recent advances and controversies. Current opinion in supportive and palliative care. 2018;12(2):148-53.

3. Eitner A, Hofmann GO, Schaible HG. Mechanisms of Osteoarthritic Pain. Studies in Humans and Experimental Models. Frontiers in molecular neuroscience. 2017;10:349.

4. Kidd B. Mechanisms of pain in osteoarthritis. HSS journal : the musculoskeletal journal of Hospital for Special Surgery. 2012;8(1):26-8.

5. Lozada CJ, Culpepper Pace SS. Osteoarthritis. Medscape. URL: https://emedicine.medscape.com/article/330487-overview. 2019.

6. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014;73(7):1323-30.

7. O´Connor MI. Sex difference of Osteoarthritis of the hip and knee. J Am Acad Orthop Surg. 2007;15 Suppl 1:S22-5.

8. United Nations. World Population to 2300. Available at: http://www.un.org/esa/population/publications/.../WorldPop2300final.pdf

9. Reginster JY, Neuprez A, Lecart MP, Sarlet N, Bruyere O. Role of glucosamine in the treatment for osteoarthritis. Rheumatol Int. 2012;32(10):2959-67.

10. Schaible HG, Schmelz M, Tegeder I. Pathophysiology and treatment of pain in joint disease. Adv Drug Deliv Rev. 2006;58(2):323-42.

11. Laupattarakasem W, Laopaiboon M, Laupattarakasem P, Sumananont C. Arthroscopic debridement for knee osteoarthritis. Cochrane Database Syst Rev. 2008(1):CD005118.

12. Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. Bmj Open. 2012;2(1): :e000435.

13. Vane JR, Bakhle YS, Botting RM. Cyclooxygenases 1 and 2. Annu Rev Pharmacol Toxicol. 1998;38:97-120.

14. Puljak L, Marin A, Vrdoljak D, Markotic F, Utrobicic A, Tugwell P. Celecoxib for osteoarthritis. The Cochrane database of systematic reviews. 2017;5:CD009865.

15. What is a Systematic Review? [09/03/2019]. Available at: https://consumers.cochrane.org/what-systematic-review

16. Cochrane Reviews. [11/03/2019]. Available at:
https://community.cochrane.org/handbook-sri/chapter-1-introduction/11-cochrane/12-systematic-reviews/122-what-systematic-review17. What is Cochrane? [11/03/2017]. Available at:
https://community.cochrane.org/handbook-sri/chapter-1-introduction/11-cochrane/111-what-is-cochrane.

18. Cochrane Database of Systematic reviews. [11/03/2019]. Available at:
https://www.cochranelibrary.com/cdsr/about-cdsr.

19. About Cochrane Reviews. [05/03/2019]. Available at:
https://www.cochranelibrary.com/about/about-cochrane-reviews.

20. Overview of reviews. [07/03/2019]. Available at.
https://training.cochrane.org/resource/overviews-reviews.

21. Cochrane C. Cochrane handbook for systematic reviews of interventions. 2008. Available at: http://handbook.cochrane.org/.

22. Karabis A, Nikolakopoulos S, Pandhi S, Papadimitropoulou K, Nixon R, Chaves RL, et al. High correlation of VAS pain scores after 2 and 6 weeks of treatment with VAS pain scores at 12 weeks in randomised controlled trials in rheumatoid arthritis and osteoarthritis: meta-analysis and implications. Arthritis Res Ther. 2016;18:73.

23. Jelicic Kadic A, Vucic K, Dosenovic S, Sapunar D, Puljak L. Extracting data from figures with software was faster, with higher interrater reliability than manual extraction. Journal of clinical epidemiology. 2016;74:119-23.

24. Cochrane C. Cochrane handbook for systematic reviews of interventions. 2008. Available at: http://handbook.cochrane.org/.

25. Introduction to RevMan. [06/03/2019]. Available at:
https://training.cochrane.org/resource/introduction-revman

26. Asmus MJ, Essex MN, Brown PB, Mallen SR. Efficacy and Tolerability of Celecoxib in Patients with Osteoarthritis Who Previously Did Not Respond to or Did Not Tolerate Naproxen and Ibuprofen: Results from 2 Identically Designed Randomized Trials. Osteoarthr Cartilage. 2013;21:S253-S.

27. Bensen WG, Fiechtner JJ, McMillen JI, Zhao WW, Yu SS, Woods EM, et al. Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial. Mayo Clin Proc. 1999;74(11):1095-105.

28. Bingham CO, 3rd, Sebba AI, Rubin BR, Ruoff GE, Kremer J, Bird S, et al. Efficacy and safety of etoricoxib 30 mg and celecoxib 200 mg in the treatment of osteoarthritis in two

identically designed, randomized, placebo-controlled, non-inferiority studies. Rheumatology (Oxford). 2007;46(3):496-507.

29. Birbara C, Ruoff G, Sheldon E, Valenzuela C, Rodgers A, Petruschke RA, et al. Efficacy and safety of rofecoxib 12.5 mg and celecoxib 200 mg in two similarly designed osteoarthritis studies. Curr Med Res Opin. 2006;22(1):199-210.

30. Boswell DJ, Ostergaard K, Philipson RS, Hodge RA, Blum D, Brown JC, et al. Evaluation of GW406381 for treatment of osteoarthritis of the knee: two randomized, controlled studies. Medscape J Med. 2008;10(11):259.

31. Clegg DO, Reda DJ, Harris CL, Klein MA, O'Dell JR, Hooper MM, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med. 2006;354(8):795-808.

32. Conaghan PG, Dickson J, Bolten W, Cevc G, Rother M. A multicentre, randomized, placebo- and active-controlled trial comparing the efficacy and safety of topical ketoprofen in Transfersome gel (IDEA-033) with ketoprofen-free vehicle (TDT 064) and oral celecoxib for knee pain associated with osteoarthritis. Rheumatology (Oxford). 2013;52(7):1303-12.

33. De Lemos BP, Xiang J, Fleming RRB. Tramadol Hydrochloride Extended-Release Once-Daily in the Treatment of Osteoarthritis of the Knee and/or Hip: A Double-Blind, Randomized, Dose-Ranging Trial. Am J Ther. 2011;18(3):216-26.

34. Essex MN, O'Connell MA, Behar R, Bao W. Efficacy and safety of nonsteroidal anti-inflammatory drugs in Asian patients with knee osteoarthritis: summary of a randomized, placebo-controlled study. Int J Rheum Dis. 2016;19(3):262-70.

35. Fleischmann R, Sheldon E, Maldonado-Cocco J, Dutta D, Yu S, Sloan VS. Lumiracoxib is effective in the treatment of osteoarthritis of the knee: a prospective randomized 13-week study versus placebo and celecoxib. Clin Rheumatol. 2006;25(1):42-53.

36. Gibofsky A, Williams GW, McKenna F, Fort JG. Comparing the efficacy of cyclooxygenase 2-specific inhibitors in treating osteoarthritis: appropriate trial design considerations and results of a randomized, placebo-controlled trial. Arthritis Rheum. 2003;48(11):3102-11.

37. Gordo AC, Walker C, Armada B, Zhou D. Efficacy of celecoxib versus ibuprofen for the treatment of patients with osteoarthritis of the knee: A randomized double-blind, non-inferiority trial. J Int Med Res. 2017;45(1):59-74.

38. Hochberg MC, Fort JG, Svensson O, Hwang C, Sostek M. Fixed-dose combination of enteric-coated naproxen and immediate-release esomeprazole has comparable efficacy to

celecoxib for knee osteoarthritis: two randomized trials. Curr Med Res Opin. 2011;27(6):1243-53.

39. Kivitz AJ, Moskowitz RW, Woods E, Hubbard RC, Verburg KM, Lefkowith JB, et al. Comparative efficacy and safety of celecoxib and naproxen in the treatment of osteoarthritis of the hip. J Int Med Res. 2001;29(6):467-79.

40. Lee M, Cho S. A Randomized, Multicenter, Phase III Trial toEvaluate the Efficacy and Safety of Polmacoxib Compared with Celecoxib and Placebo for Patients with Osteoarthritis. Clin Orthop Surg. 2017;9(4):439-57.

41. Lehmann R, Brzosko M, Kopsa P, Nischik R, Kreisse A, Thurston H, et al. Efficacy and tolerability of lumiracoxib 100 mg once daily in knee osteoarthritis: a 13-week, randomized, double-blind study vs. placebo and celecoxib. Curr Med Res Opin. 2005;21(4):517-26.

42. McKenna F, Borenstein D, Wendt H, Wallemark C, Lefkowith JB, Geis GS. Celecoxib versus diclofenac in the management of osteoarthritis of the knee. Scand J Rheumatol. 2001;30(1):11-8.

43. Pincus T, Koch G, Lei H, Mangal B, Sokka T, Moskowitz R, et al. Patient Preference for Placebo, Acetaminophen (paracetamol) or Celecoxib Efficacy Studies (PACES): two randomised, double blind, placebo controlled, crossover clinical trials in patients with knee or hip osteoarthritis. Ann Rheum Dis. 2004;63(8):931-9.

44. Reginster JY, Dudler J, Blicharski T, Pavelka K. Pharmaceutical-grade Chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis: the ChONdroitin versus CElecoxib versus Placebo Trial (CONCEPT). Ann Rheum Dis. 2017;76(9):1537-43.

45. Rother M, Lavins BJ, Kneer W, Lehnhardt K, Seidel EJ, Mazgareanu S. Efficacy and safety of epicutaneous ketoprofen in Transfersome (IDEA-033) versus oral celecoxib and placebo in osteoarthritis of the knee: multicentre randomised controlled trial. Ann Rheum Dis. 2007;66(9):1178-83.

46. Schnitzer TJ, Dattani ID, Seriolo B, Schneider H, Moore A, Tseng L, et al. A 13-week, multicenter, randomized, double-blind study of lumiracoxib in hip osteoarthritis. Clin Rheumatol. 2011;30(11):1433-46.

47. Sheldon E, Beaulieu A, Paster Z, Dutta D, Yu S, Sloan VS. Efficacy and tolerability of lumiracoxib in the treatment of osteoarthritis of the knee: a 13-week, randomized, double-blind comparison with celecoxib and placebo. Clin Ther. 2005;27(1):64-77.

48. Smugar SS, Schnitzer TJ, Weaver AL, Rubin BR, Polis AB, Tershakovec AM. Rofecoxib 12.5 mg, rofecoxib 25 mg, and celecoxib 200 mg in the treatment of symptomatic osteoarthritis: results of two similarly designed studies. Curr Med Res Opin. 2006;22(7):1353-67.
49. Tannenbaum H, Berenbaum F, Reginster JY, Zacher J, Robinson J, Poor G, et al. Lumiracoxib is effective in the treatment of osteoarthritis of the knee: a 13 week, randomised, double blind study versus placebo and celecoxib. Ann Rheum Dis. 2004;63(11):1419-26.
50. Williams GW, Ettlinger RE, Ruderman EM, Hubbard RC, Lonien ME, Yu SS, et al. Treatment of osteoarthritis with a once-daily dosing regimen of celecoxib: a randomized, controlled trial. J Clin Rheumatol. 2000;6(2):65-74.
51. Williams GW, Hubbard RC, Yu SS, Zhao W, Geis GS. Comparison of once-daily and twice-daily administration of celecoxib for the treatment of osteoarthritis of the knee. Clin Ther. 2001;23(2):213-27.
52. Wittenberg RH, Schell E, Krehan G, Maeumbaed R, Runge H, Schluter P, et al. First-dose analgesic effect of the cyclo-oxygenase-2 selective inhibitor lumiracoxib in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled comparison with celecoxib [NCT00267215]. Arthritis Res Ther. 2006;8(2):R35.
53. Bianchi M, Broggini M. A randomised, double-blind, clinical trial comparing the efficacy of nimesulide, celecoxib and rofecoxib in osteoarthritis of the knee. Drugs. 2003;63 Suppl 1:37-46.
54. Bianchi M, Broggini M, Balzarini P, Franchi S, Sacerdote P. Effects of nimesulide on pain and on synovial fluid concentrations of substance P, interleukin-6 and interleukin-8 in patients with knee osteoarthritis: comparison with celecoxib. Int J Clin Pract. 2007;61(8):1270-7.
55. Detrembleur C, De Nayer J, van den Hecke A. Celecoxib improves the efficiency of the locomotor mechanism in patients with knee osteoarthritis. A randomised, placebo, double-blind and cross-over trial. Osteoarthritis Cartilage. 2005;13(3):206-10.
56. Gallelli L, Galasso O, Falcone D, Southworth S, Greco M, Ventura V, et al. The effects of nonsteroidal anti-inflammatory drugs on clinical outcomes, synovial fluid cytokine concentration and signal transduction pathways in knee osteoarthritis. A randomized open label trial. Osteoarthr Cartilage. 2013;21(9):1400-8.
57. Leeb BF, Bucsi L, Keszthelyi B, Bohmova J, Valesova M, Hawel R, et al. [Treatment of osteoarthritis of the knee joint. Efficacy and tolerance to acemetacin slow release in

comparison to celecoxib]. Orthopade. 2004;33(9):1032-41. Behandlung der Gonarthrose. Wirksamkeit und Vertraglichkeit von retardiertem Acemetacin im Vergleich zu Celecoxib.
58. Van Helvoort EM, Coeleveld K, de Boer TN, Huisman AM, Polak AA, Bijlsma JWJ, et al. Lack of a Clear Disease Modifying Activity of Celecoxib in Treatment of End-Stage Knee Osteoarthritis: A Randomized Observer Blinded Clinical Trial. Annals of the Rheumatic Diseases. 2017;76:968.
59. Ozgocmen S, Ardicoglu O, Erdogan H, Fadillioglu E, Gudul H. In vivo effect of celecoxib and tenoxicam on oxidant/anti-oxidant status of patients with knee osteoarthritis. Ann Clin Lab Sci. 2005;35(2):137-43.
60. Sampalis JS, Brownell LA. A randomized, double blind, placebo and active comparator controlled pilot study of UP446, a novel dual pathway inhibitor anti-inflammatory agent of botanical origin. Nutr J. 2012;11:21.
61. Simon LS, Lanza FL, Lipsky PE, Hubbard RC, Talwalker S, Schwartz BD, et al. Preliminary study of the safety and efficacy of SC-58635, a novel cyclooxygenase 2 inhibitor - Efficacy and safety in two placebo-controlled trials in osteoarthritis and rheumatoid arthritis, and studies of gastrointestinal and platelet effects. Arthritis Rheum-Us. 1998;41(9):1591-602.
62. Tascioglu F, Aydemir A, Öner C. Comparison of the efficacy of Celecoxib and Diclofenac Sodium in the Treatment of Knee Osteoarthritis. Türk Fiz Tip Rehab Derg. 2004.
63. Trudeau J, Van Inwegen R, Eaton T, Bhat G, Paillard F, Ng D, et al. Assessment of pain and activity using an electronic pain diary and actigraphy device in a randomized, placebo-controlled crossover trial of celecoxib in osteoarthritis of the knee. Pain Pract. 2015;15(3):247-55.
64. Bingham CO, Smugar SS, Wang HW, Tershakovec AM. Early response to COX-2 inhibitors as a predictor of overall response in osteoarthritis: pooled results from two identical trials comparing etoricoxib, celecoxib and placebo. Rheumatology. 2009;48(9):1122-7.
65. Pergolizzi J, Ahlbeck K, Aldington D, Alon E, Coluzzi F, Dahan A, et al. The development of chronic pain: physiological CHANGE necessitates a multidisciplinary approach to treatment. Curr Med Res Opin. 2013;29(9):1127-35.
66. Phillips CJ. The Cost and Burden of Chronic Pain. Rev Pain. 2009;3(1):2-5.
67. Taylor SD, Everett SV, Taylor TN, Watson DJ, Taylor-Stokes G. A measure of treatment response: patient and physician satisfaction with traditional NSAIDs for osteoarthritis control. Open Access Rheumatol. 2013;5:69-76.
68. Conaghan PG, Peloso PM, Everett SV, Rajagopalan S, Black CM, Mavros P, et al. Inadequate pain relief and large functional loss among patients with knee osteoarthritis:

evidence from a prospective multinational longitudinal study of osteoarthritis real-world therapies. Rheumatology. 2015;54(2):270-7.

69. Copsey B, Buchanan J, Fitzpatrick R, Lamb SE, Dutton SJ, Cook JA. Duration of Treatment Effect Should Be Considered in the Design and Interpretation of Clinical Trials: Results of a Discrete Choice Experiment. Med Decis Making. 2019:272989X19841877.

70. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. The Cochrane database of systematic reviews. 2017;2:MR000033.